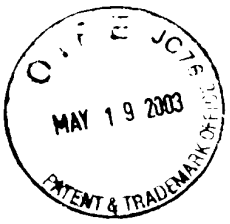


PATENT
Attorney Docket **054800-5008-01**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Amy Arrow *et al.***

Application No. **09/211,794**

Filed: **December 15, 1998**

For: **Three Component Chimeric Antisense Oligonucleotides**

Examiner: **Mary M. Schmidt**

Group Art Unit: **1635**

AMENDMENT UNDER 37 C.F.R. 1.111

In response to the Office Action dated November 19, 2002, the period for response having been extended to May 19, 2003 by the accompanying petition for a three-month extension of time, please consider the following remarks responding to the claim rejections.

Summary of the Office Action

1. Claim 18 was rejected under 35 U.S.C. 112 (first paragraph) was rejected as purportedly not being enabled by the disclosure of the specification.

2. Claims 1-19 were rejected under 35 U.S.C. 103(a) as being unpatentable over Monia *et al.* (U.S. Patent 5,576,208), Milligan *et al.* (J. Med. Chem. 36, 1923-1937) and Matulic-Adamic *et al.* (U.S. Patent 5,998,203).

Rejection under 35 U.S.C. 112 (first paragraph)

Claim 18 was rejected under 35 U.S.C. 112 (first paragraph) as purportedly not being enabled, because the specification, while being enabled for methods of cleaving RNA *in vitro* does not reasonably provide enablement for methods of cleaving whole RNA *in vitro*. Before addressing the merits of the rejection, Applicants bring to the Examiner's attention that claim 18 of the present application contains all the limitations of claim 20 in U.S. Patent 5,849,902 of which the present application is a continuation thereof. It is unclear to the Applicants how the Examiner can maintain an enablement rejection under these circumstances.

Applicants submit that the rejection is without merit because in raising the rejection, the Examiner has cited references that provide evidence that factors such as oligonucleotide stability, etc. are unpredictable. The flaw in the Examiner's logic is that the cited references do not describe the use of oligonucleotides having the structure set forth in claim 18. The novel structures of the claimed oligonucleotides were specifically engineered to address and rectify the deficiencies of the

oligonucleotides described in the cited references. As such, the Examiner's reliance on these references appears to be mistaken and any enablement rejection based on such should be withdrawn.

The legal standard of enablement simply requires that a specification disclose sufficient information to enable those skilled in the art to make and use the claimed invention (see *Hormone Research Foundation v. Genetech*, 15 USPQ2d 1039, 1047). Furthermore, enablement is not precluded by the necessity of some experimentation such as routine screening. However, the experimentation must not be undue (see In re Wands, 858 F.2d 731, 736-737). The fact that experimentation may be complex doesn't necessarily make it undue, if the art typically engages in such experimentation (see *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174). In the present instance, those skilled in the art would have clearly understood that *in vitro* or *in vivo* efficacy of the claimed oligonucleotides could be rapidly tested using simple "plus/minus" assays similar to those taught in the present specification. The Examiner cannot credibly contend that such facile tests for efficacy could somehow constitute undue experimentation. Absent a demonstration of undue experimentation, the Examiner has failed to establish that claim 18 is not enabled, and the rejection under 35 U.S.C. 112 (first paragraph) should be withdrawn.

Applicants submit that it is incumbent upon the Examiner to provide a well-reasoned explanation as to why the claimed invention cannot be expected to function (see *In re Marzocchi*, 439 F.2d 220, 223). In the present instance, the specification provides direct *in vitro* evidence that the claimed invention indeed functions as claimed. Conversely, the Examiner has not provided <u>any</u> relevant evidence that conclusively contradicts the data presented in the application. Instead, the Examiner has attempted to summarily dismiss the teachings in the specification by embracing commentary in the cited references that is not germane to the presently claimed invention. In view of this fact, Applicants submit that the Examiner has failed to provide any evidence that conclusively establishes that the presently claimed invention is not functional. Absence such evidence, the Examiner has also failed to establish that claim 18 is not enabled and the rejection under 35 U.S.C. 112 (first paragraph) should be withdrawn.

<u>Rejection under 35 U.S.C. 103</u>

Claims 1-19 were rejected under 35 U.S.C. 103(a) as being unpatentable over Monia *et al.*, Milligan *et al.* and Matulic-Adamic *et al.* Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in

the knowledge generally available to one of ordinary skill in the art (see *In re Kotzab*, 217 F.3d 1365, 1370; *In re Fine*, 837 F.2d 1071; and *In re Jones*, 958 F.2d 347). The Examiner cites claim 1 of this reference as disclosing 5' and/or 3' cap structures (see Office Action at page 12, lines 1-3) further citing the specification as disclosing "that such modifications may be used on both RNA and single stranded DNA" (see Office Action at page 12, lines 3-5). The Examiner is incorrect in her reading of the specification in this instance. The cited passage indicates that the modified nucleic acids disclosed in the cited reference are "particularly useful for enzymatic cleavage of RNA or single-stranded DNA" (see Matulic-Adamic *et al.* at column 2, lines 46-47). The cited reference therefore does not disclose these modifications on single stranded DNA, but rather discloses double-stranded hairpin ribozyme structures unrelated to the claimed oligonucleotides of the invention. Thus, this reference does not disclose modification of single stranded DNA as purported by the Examiner and is unrelated to the claimed antisense oligonucleotides of the invention.

The Examiner relies on Matulic-Adamic *et al.* for the purported disclosure of 5' and/or 3' cap structures such as inverted abasic moieties. As discussed above, this reference discloses only modification of ribozymes (*i.e.*, nucleic acids with enzymatic capability that do not require the presence of an enzyme). This reference does not make any mention of oligonucleotides, let alone modification of oligonucleotides at the 5'or 3' terminus. Furthermore, the claimed oligonucleotides comprise an RNase H activating region to which RNase H binds and cleaves the target nucleic acid, and therefore are unrelated to the ribozyme nucleic acids disclosed in Matulic-Adamic *et al.* which do not require the presence of an enzyme to cleave the target nucleic acid. The skilled artisan would therefore not be motivated to combine the Matulic-Adamic *et al.* reference with the remaining cited references.

In the absence of any disclosure related to antisense oligonucleotides in the Matulic-Adamic *et al.* reference, Applicants submit that there would be no motivation to combine the Matulic-Adamic *et al.* reference with the Monia *et al.* or Milligan *et al.* references. More specifically, because the Matulic-Adamic *et al.* reference relates to ribozyme structures while the remaining references relate to oligonucleotide structures, the skilled artisan would not be motivated to combine these references to arrive at the claimed antisense oligonucleotides.

Furthermore, in the absence of the Matulic-Adamic *et al.* reference, the remaining two references do not render the claimed invention obvious because they do not disclose or suggest all the limitations of the claims. These references were considered during prosecution of the parent applications (now U.S. Patents 5,849,902 and 5,989,912) where broader claims were allowed directed to the same chimeric

antisense oligonucleotides and methods of use. The obvious-type double patenting rejection made by the Examiner in the Office Action dated March 30, 2000 confirms that the pending claims are indeed directed to closely related subject matter to that allowed in the above-referenced patents.

Finally, with regard to the method of claim 18, Applicants bring to the attention of the Examiner that claim 18 was rejected for lack of enablement under 35 U.S.C. 112 (first paragraph). It is unclear to the Applicants how the claimed method is not enabled by the specification, if at the same time as the Examiner purports, the skilled artisan would have a reasonable expectation of success of arriving at the claimed method based on the disclosure of the cited references. These positions are contrary to each other as it is not possible for the specification to lack enablement when there is a reasonable expectation of success at producing the claimed invention based on the level of skill in the art.

In view of the above remarks, Applicants request withdrawal of the rejection of claims 1-19 as being obvious under 35 U.S.C. 103(a).

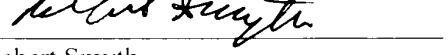
Conclusion

Applicants respectfully request reconsideration and the timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, she is invited to telephone the undersigned at her convenience.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Dated: **May 19, 2003**
Morgan, Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Ave., NW
Washington, D.C. 20004
202-739-3000

Respectfully submitted
Morgan, Lewis & Bockius LLP



Robert Smyth
Registration No. 50,801